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Supplementary appendix

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Clinical and virological data of the first cases of COVID-19 in Europe: a case series.

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Materials and Methods

Participants and source of data

According to the criteria used, a confirmed case is defined as any possible case who has a positive SARS-CoV-2(1) RT-PCR on respiratory samples (performed by an accredited laboratory). Up to January 24, 2020, a possible case was defined as follows: (1) any patient with clinical signs consistent with severe acute lower respiratory infection requiring admission to hospital, with no other etiology that fully explains the clinical presentation, AND with a history of travel to or residence in the city of Wuhan, Hubei Province, China, within the 14 days prior to symptom onset; (2) any patient with any acute respiratory illness, whatever the severity, AND with history of at least one of the following exposures within the 14 days prior to illness onset: close contact with a confirmed case of COVID-19, while symptomatic; OR having shared the same at-risk exposures as a confirmed case of COVID-19 (i.e. history of travel to or residence in the city of Wuhan, Hubei Province, China) OR having worked in or attended a health care facility where patients with COVID-19 have been reported OR having visited or worked in a live animal market in Wuhan, Hubei Province, China.

Clinical, biological and radiological data were carefully recorded from computerized medical records, while a network of involved clinicians was implemented since the onset of the first cases identified in France. We used the open-source ‘Clinical Characterization Protocol for Severe Emerging Infections’ of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), supported by the World Health Organization

(WHO)(2), which has been updated in response to COVID-19. All patients were hospitalized in an isolation room according to French policy for suspected or confirmed cases.

Epidemiological data were collected onto standardized forms through interviews of infected persons, and contacts and relatives when possible, that were conducted by physicians from Regional Health Agencies and the National Public Health Agency (*Santé Publique France*). We collected information on the dates of contact at risk, date of illness onset and details on travels in France.

The illness severity was defined, according to WHO criteria for severe pneumonia in adults (WHO/nCoV/Clinical/2020.2 (3)) as fever or suspected respiratory infection, plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO₂ <90% on room air). The Acute Respiratory Distress Syndrome was defined, according to WHO criteria : (1) new or worsening respiratory symptoms within one week of known clinical insult; (2) bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules; (3) respiratory failure not fully explained by cardiac failure or fluid overload; (4) 200 mmHg < PaO₂/FiO₂ ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH₂O, 7 or non-ventilated).

RNA extraction and real-time RT-PCR

RNA extraction was performed with the Extraction NucleoSpin Dx Virus kit (Macherey Nagel), or by the automated NucliSENS® easyMAG® (BioMérieux, Marcy l'Etoile, France) using manufacturer's instructions. For RdRp-IP1 RT-PCR (Table S1), used for detection, RNA was extracted from 100 µl of specimen or culture supernatant and eluted in 100 µl of water and used as a template for real-time (rt) RT-PCR. A 25 µL reaction contained 5 µL of RNA, 12.5 µL of 2X reaction buffer provided with the Superscript III one step RT-PCR system with Platinum Taq Polymerase (Invitrogen, Darmstadt, Germany; containing 0.4 mM of each dNTPs and 3 mM magnesium sulfate), 1 µL of reverse transcriptase/ Taq mixture from the kit, 0.4 µL of a 50 mM magnesium sulfate solution (Invitrogen). Thermal cycling was performed at 55°C for 20 min for reverse transcription, followed by 95°C for 3 min and then 50 cycles of 95°C for 15 s, 58°C for 30 s, on a Light Cycler 480 (96) thermocycler (Roche) or on the QuantStudio5 rtPCR Systems (Thermo Fisher Scientific). For RdRp quantitative RT-PCR, RNA extraction was performed on the EMAG® platform (Biomerieux, Marcy-l'Étoile, France), using manufacturer's instructions. RNA was extracted from 200 µl of sample eluted in 50 µl of elution buffer. The RdRp gene RT-PCR corresponds to the Charité protocol (4) using primers RdRP_SARSr-F2 and -R1 and the RdRP_SARSr-P2 (Table S1). Amplification was performed using QuantStudio 5 rtPCR Systems (Thermo Fisher Scientific, Waltham, Massachusetts, USA).

When a sample (respiratory samples, plasma or stool) was positive with RdRp-IP1, quantification of the number of RNA copies was done according to a scale ranging from 10³ to 10⁶ copies/µL. The viral load in stools was calculated as previously described (5) and expressed in number of RNA copies/g of stool. The quality of nasopharyngeal swabs was checked using the CELL Control r-gene® kit (BioMérieux). This kit is provided with quantified plasmid for cellular quantification. All viral loads for respiratory samples were calculated as described above and normalized according the cellular quantification as the number of RNA copies/1 000 cells. All positive plasma samples were quantified and expressed as number of RNA copies/mL.

Primers and probes

Primer and probe sequences (Eurogentec, Seraing, Belgium) are shown in Supplementary Table S1. They either correspond to the RdRp or E gene assay from the Charité protocol (4) or to the RdRp-IP1 assay designed at Institut Pasteur to target the RdRp gene spanning nt 12669-12759 (positions according SARS-CoV, NC_004718) based

on the first sequences of SARS-CoV-2 made available on the GISAID database on January 11, 2020 (Supplementary Table S2).

High Throughput virus sequencing

RNA from specimens or from virus culture was extracted using the RNeasy mini kit (Qiagen, Courtaboeuf, France), and 100µl of sample mixed with 350µl RLT lysis buffer was incubated at 70°C for 5 minutes for virus inactivation. Extraction was performed according to the manufacturer's instructions and RNA was purified on SPRI beads RNA clean XP (Beckman Coulter, Brea, California, USA). cDNA was synthesized using the Maxima H Minus First Strand cDNA Synthesis Kit (Thermo Fisher Scientific, Waltham, Massachusetts, USA) according to the manufacturer's instructions and purified again on SPRI beads RNA clean XP. Purified cDNA was sequenced on the P2M platform at Institut Pasteur. In brief, Nextera XT DNA Library Preparation® kit (Illumina, San Diego, California, USA) was used for library construction. The pooled libraries were sequenced on an Illumina NextSeq 500® instrument using a paired-end 150 bp run. The fastq files were generated and de-multiplexed with the bcl2fastq Conversion Software® v2.20 (Illumina). Data analyses were performed with CLC Genomics Workbench® 20. Consensus sequences were deposited in the GISAID database (<https://www.gisaid.org/>).

Virus isolation and virus titration

All experiments were conducted under strict BSL3 conditions. Vero E6 cells (mycoplasma-free) seeded in 12-well plates (4×10^5 cells/well) were cultured in DMEM (Thermo Fisher Scientific) containing 1% PS (Penicillin 10,000 U/mL; Streptomycin 10,000 µg/mL) and supplemented with 5% FBS (Fetal Bovine Serum). Respiratory specimens were diluted 1:2 with DMEM 1% PS without FBS and supplemented with 1µg/ml TPCK-trypsin (Sigma-Aldrich, St Louis, Missouri, USA), added to the cells and incubated for one hour at 37°C in the presence of 5% CO₂. The inoculum was then removed and replaced with fresh DMEM 1% PS containing 1µg/mL TPCK-trypsin. After incubation for three days at 37°C in the presence of 5% CO₂, cells were observed for the presence of a cytopathic effect (CPE) under the microscope and culture supernatants were harvested, aliquoted and stored at -80°C. Virus titration was performed on Vero E6 cells in a standard plaque assay adapted from Matrosovich *et al* (6).

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Table S1 - RT-PCR for the detection of SARS-CoV-2: primers and probes used

Name	Sequences	PCR product	Ref.
<i>RdRp gene / Charité</i>			
<i>RdRP_SARSr-F2</i>	GTGARATGGTCATGTGTGGCGG	100 bp	(4)
<i>RdRP_SARSr-R1</i>	CARATGTTAAASACACTATTAGCATA		
<i>RdRP_SARSr-P2</i>	[5']Fam -CAGGTGGAACCTCATCAGGAGATGC-[3']BBQ		
<i>E gene / Charité</i>			
E_Sarbeco_F1	ACAGGTACGTTAATAGTTAATAGCGT	125 bp	(4)
E_Sarbeco_R2	ATATTGCAGCAGTACGCACACA		(4)
E_Sarbeco_P1	ACACTAGCCATCCTTACTGCGCTTCG [5']Fam [3']BHQ-1		(4)
<i>RdRp gene/n CoV_IP1</i>			
RdRp_nCoV_IP1-12669Fw	AGAGATGTTGACACAGAC	125 bp	NRCRV NRCRV NRCRV
RdRp_nCoV_IP1-12759Rv	ACTAGACCTTGAGATGCATA		
RdRp_nCoV_IP1-12696bProbe(+)	[5']Fam – AACACACAACAGCATCGTCA - [3']BHQ-1		

NRCRV: National Reference Center for Respiratory Viruses, Institut Pasteur, Paris, France

Table S2 - SARS-CoV-2 names and sequences

We gratefully acknowledge the Authors, the Originating and Submitting Laboratories for their sequence and metadata shared through GISAID, on which this research is based.

Accession ID	Virus name	Location	Collection date	Originating lab	Submitting lab	Authors
EPI_ISL_402119	BetaCoV/Wuhan/IVDC-HB-01/2019	Asia / China / Hubei / Wuhan	2019-12-30	National Institute for Viral Disease Control and Prevention, China CDC	National Institute for Viral Disease Control and Prevention, China CDC	Wenjie Tan, Xiang Zhao, Wenling Wang, Xuejun Ma, Yongzhong Jiang, Roujian Lu, Ji Wang, Weimin Zhou, Peihua Niu, Peipei Liu, Faxian Zhan, Weifeng Shi, Baoying Huang, Jun Liu, Li Zhao, Yao Meng, Xiaozhou He, Fei Ye, Na Zhu, Yang Li, Jing Chen, Wenbo Xu, George F. Gao, Guizhen Wu
EPI_ISL_402121	BetaCoV/Wuhan/IVDC-HB-05/2019	Asia / China / Hubei / Wuhan	2019-12-30	National Institute for Viral Disease Control and Prevention, China CDC	National Institute for Viral Disease Control and Prevention, China CDC	Wenjie Tan, Xuejun Ma, Xiang Zhao, Wenling Wang, Yongzhong Jiang, Roujian Lu, Ji Wang, Peihua Niu, Weimin Zhou, Faxian Zhan, Weifeng Shi, Baoying Huang, Jun Liu, Li Zhao, Yao Meng, Fei Ye, Na Zhu, Xiaozhou He, Peipei Liu, Yang Li, Jing Chen, Wenbo Xu, George F. Gao, Guizhen Wu
EPI_ISL_402120	BetaCoV/Wuhan/IVDC-HB-04/2020	Asia / China / Hubei / Wuhan	2020-01-01	National Institute for Viral Disease Control and Prevention, China CDC	National Institute for Viral Disease Control and Prevention, China CDC	Wenjie Tan, Xiang Zhao, Wenling Wang, Xuejun Ma, Yongzhong Jiang, Roujian Lu, Ji Wang, Weimin Zhou, Peihua Niu, Peipei Liu, Faxian Zhan, Weifeng Shi, Baoying Huang, Jun Liu, Li Zhao, Yao Meng, Xiaozhou He, Fei Ye, Na Zhu, Yang Li, Jing Chen, Wenbo Xu, George F. Gao, Guizhen Wu
EPI_ISL_402123	BetaCoV/Wuhan/IPBCA MS-WH-01/2019	Asia / China / Hubei / Wuhan	2019-12-24	Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College	Institute of Pathogen Biology, Chinese Academy of Medical Sciences & Peking Union Medical College	Lili Ren, Jianwei Wang, Qi Jin, Zichun Xiang, Zhiqiang Wu, Chao Wu, Yiwei Liu
EPI_ISL_402124	BetaCoV/Wuhan/WIV04/2019	Asia / China / Hubei / Wuhan	2019-12-30	Wuhan Jinyintan Hospital	Wuhan Institute of Virology, Chinese Academy of Sciences	Peng Zhou, Xing-Lou Yang, Ding-Yu Zhang, Lei Zhang, Yan Zhu, Hao-Rui Si, Zhengli Shi
EPI_ISL_402125	BetaCoV/Wuhan-Hu-1/2019	Asia / China	2019-12	unknown	National Institute for Communicable Disease Control and Prevention (ICDC) Chinese Center for Disease Control and Prevention (China CDC)	Zhang,Y.-Z., Wu,F., Chen,Y.-M., Pei,Y.-Y., Xu,L., Wang,W., Zhao,S., Yu,B., Hu,Y., Tao,Z.-W., Song,Z.-G., Tian,J.-H., Zhang,Y.-L., Liu,Y., Zheng,J.-J., Dai,F.-H., Wang,Q.-M., She,J.-L. and Zhu,T.-Y.

Supplementary Fig. S1 - Case #1 - chest X-rays and lung CT-scan from the day after the diagnosis day (illness day 8)

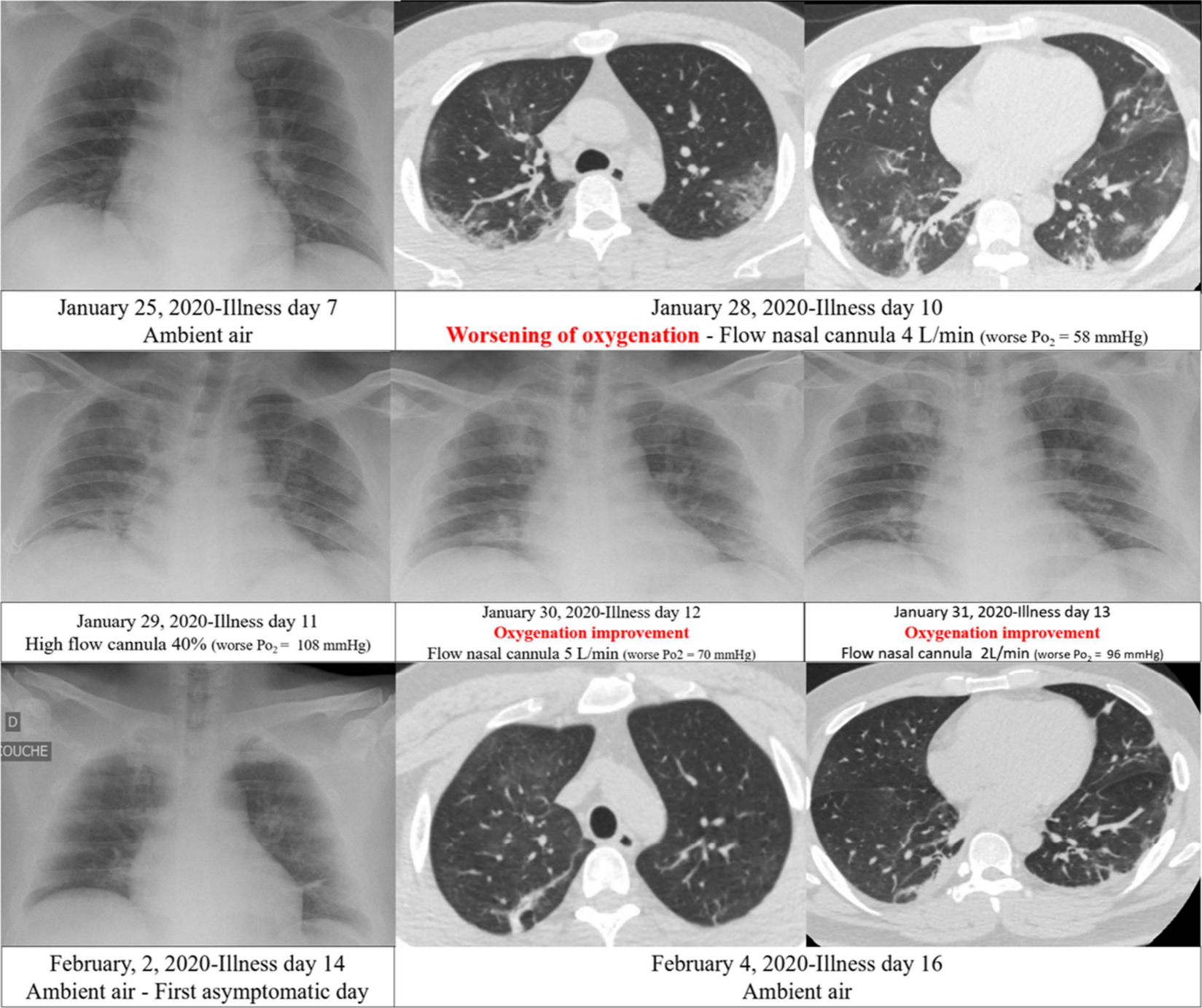


Table S3-1 - Case #1 - Baseline characteristics and their changes over time

Case #1	Diagnosis day January 24 Illness day 6	January 25 Illness day 7	January 26 Illness day 8	January 27 Illness day 9	January 28 Illness day 10	January 29 Illness day 11	January 30 Illness day 12	January 31 Illness day 13	February 1 Illness day 14	Asymptomatic day February 2 Illness day 15	Asymptomatic day February 3 Illness day 16	February 4	February 5	February 6	February 7	February 8	February 9	February 10	February 11	February 12 Discharge day
Setting	WARD	WARD	WARD	WARD	WARD/I CU	ICU	ICU	ICU/ WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD
Symptoms																				
Any of the following symptoms	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Fever	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Highest temperature, °C	39·1	40·1	39·8	39·6	39·1	39·9	37·8	37·1	37·0	37·3	37·3	37·2	37·1	36·8	36·8	36·8	37·1	36·0	37·0	37·0
Cough	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Shortness of breath	-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever, cough, shortness of breath	-	-	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia or fatigue	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rhinorrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea and vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctivitis	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biological variables																				
White blood cell counts, 10 ⁹ /L	5.8	ND	ND	ND	8	6.1	6.3	6.1	7.3	7.4	ND	10.3	ND	13.6	ND	11.2	ND	9.1	ND	8.7
Neutrophil count, 10 ⁹ /L	4.7	ND	ND	ND	6.5	4.7	4.5	4.4	5.0	5.2	ND	8.0	ND	9.8	ND	8.1	ND	6.1	ND	5.1
Lymphocyte count, 10 ⁹ /L	1	ND	ND	ND	1.1	1.2	1.3	1.2	1.6	1.5	ND	1.7	ND	2.6	ND	2.5	ND	2.3	ND	2.8
Hemoglobin, g/l	15.5	ND	ND	ND	14.1	13.6	13.9	13.8	14.6	13.4	ND	14.1	ND	13.1	ND	12.9	ND	12.3	ND	12.5
Platelet count, 10 ⁹ /L	148	ND	ND	ND	197	221	279	329	396	380	ND	521	ND	486	ND	408	ND	371	ND	335
Prothrombin time, s	17	ND	ND	ND	20	18	18	18	21	20	ND	23	ND	23	ND	20	ND	19	ND	ND
Albumin, g/L	37	ND	ND	ND	32	30	32	32	32	30	ND	31	ND	33	ND	32	ND	31	ND	32
Creatinine kinase, UI/L	122	ND	ND	ND	338	303	207	179	173	155	ND	117	ND	116	ND	66	ND	87	ND	83
Alanine aminotransferase, UI/L	37	ND	ND	ND	46	61	82	63	155	194	ND	152	ND	110	ND	92	ND	80	ND	84
Aspartate aminotransferase, U/L	32	ND	ND	ND	46	50	61	90	195	97	ND	57	ND	50	ND	38	ND	34	ND	43
Total bilirubin, mmol/L	7	ND	ND	ND	10	10	9	9	11	12	ND	10	ND	8	ND	9	ND	10	ND	11
Sodium, mmol/L	140	ND	ND	ND	132	136	137	140	140	143	ND	139	ND	144	ND	139	ND	138	ND	136
Potassium, mmol/L	4.3	ND	ND	ND	4.1	4.5	4.7	5	4.4	4.5	ND	46	ND	5.1	ND	4.7	ND	4.2	ND	4.2
Urea, mmol/L	2.8	ND	ND	ND	2.4	2.5	3.9	3.4	3.1	3	ND	3.5	ND	2.9	ND	4.2	ND	4.4	ND	4
Creatinine, μmol/L	44	ND	ND	ND	70	60	72	62	50	49	ND	60	ND	87	ND	66	ND	87	ND	83
C-reactive protein	7	ND	ND	ND	78	83	45	22	17	10	ND	<5	ND	<5	ND	<5	ND	<5	ND	<5
Lactate UI/L	ND	ND	ND	ND	1.11	0.77	0.91	0.73	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Chest X-ray and CT findings	X-ray			CT	X-ray	X-ray	X-ray			X-ray		CT								
Unilateral pneumonia																				
Bilateral pneumonia	+				+	+	+			-										
Multiple mottling and ground-glass opacity				+	-	-	-			-		+								
Treatment																				
Oxygen therapy	Ambient air	Ambient air	Ambient air	FNC (4L/min)	HFNC (40%)	FNC (5L/min)	FNC (2L/min)	FNC (2L/min)	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air
Remdesivir						J1 Loading dose	J2	J3	J4	J5										

ND = not determined

Table S3-2 - Case #2 - Baseline characteristics and their changes over time

Case #2 -	January 23 Illness day 8	Diagnosis day January 24 Illness day 9	January 25 Illness day 10	January 26 Illness day 11	January 27 Illness day 12	January 28 Illness day 13	January 29 Illness day 14	January 30 Illness day 15	January 31 Illness day 16	February 1 Illness day	February 2 Illness day 17	February 3 Illness day 18	February 4 Illness day 19	February 5 Illness day 20	February 6 Illness day 21	February 7 Illness day 22	February 8	February 9	February 10	February 11	February 12	February 13 Discharge day
Setting	ICU	ICU	ICU	ICU	ICU	ICU/ WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD
Symptoms																						
Any of the following symptoms	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fever	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Highest temperature, °C	37.5	38	38.8	38.4	38.4	37.4	37.3	37.1	37.4	37.2	36.9	36.7	37.5	37.3	37.7	37.4	37.4	37.1	37.2	37.5	37.2	36.7
Cough	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Shortness of breath	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever, cough, shortness of breath	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia or fatigue	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rhinorrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea and vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctivitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-
Biological variables																						
White blood cell counts, 10 ⁹ /L	4	ND	5.4	ND	ND	ND	ND	5.8	ND	8.7	ND	10.5	ND	8.2	ND	7.8	ND	6.2	ND	5.1	ND	ND
Neutrophil count, 10 ⁹ /L	1.81	ND	ND	ND	ND	ND	ND	3.28	ND	5.98	ND	7.65	ND	5.48	ND	ND	ND	4	ND	ND	ND	ND
Lymphocyte count, 10 ⁹ /L	1.64	ND	ND	ND	ND	ND	ND	1.84	ND	2	ND	1.9	ND	2	ND	ND	ND	1.6	ND	ND	ND	ND
Hemoglobin, g/l	16.9	ND	16.6	ND	ND	ND	ND	15.8	ND	16.3	ND	16.9	ND	16.4	ND	17	ND	16.9	ND	16.7	ND	ND
Platelet count, 10 ⁹ /L	182	ND	182	ND	ND	ND	ND	297	ND	390	ND	432	ND	433	ND	398	ND	401	ND	332	ND	ND
Prothrombin time, s	10.6	ND	12.3	ND	ND	ND	ND	ND	ND	12.5	ND	ND	ND	ND	ND	ND	ND	15	ND	16	ND	ND
Albumin, g/L	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Creatinine kinase, UI/L	147	ND	246	ND	ND	ND	ND	72	ND	107	ND	ND	ND	ND	ND	140	ND	95	ND	130	ND	ND
Alanine aminotransferase, UI/L	22	ND	21	ND	ND	ND	ND	25	ND	40	ND	47	ND	49	ND	43	ND	39	ND	49	ND	ND
Aspartate aminotransferase, U/L	32	ND	35	ND	ND	ND	ND	32	ND	40	ND	47	ND	35	ND	36	ND	34	ND	41	ND	ND
Total bilirubin, mmol/L	7	ND	10	ND	ND	ND	ND	9	ND	8	ND	6	ND	7	ND	8	ND	14	ND	14	ND	ND
Sodium, mmol/L	139	ND	131	ND	ND	ND	ND	140	ND	137	137	134	ND	137	ND	139	139	141	ND	140	ND	ND
Potassium, mmol/L	3.7	ND	3.3	ND	ND	ND	ND	3.6	ND	3.6	3.6	4.1	ND	3.5	ND	3.6	3.6	3.7	ND	3.6	ND	ND
Urea, mmol/L	4.4	ND	3.2	ND	ND	ND	ND	2.6	ND	4	4.2	3.7	ND	4	ND	4.1	3.7	3.6	ND	4.3	ND	ND
Creatinine, μmol/L	68	ND	72	ND	ND	ND	ND	72	ND	111	75	70	ND	68	ND	70	68	73	ND	80	ND	ND
C-reactive protein	ND	ND	7.7	ND	ND	ND	ND	ND	ND	8.3	6.1	11.1	ND	11.2	ND	8.4	ND	6	ND	2.8	ND	ND
Lactate UI/L	ND	ND	1.6	ND	ND	ND	ND	ND	ND	ND	0.9	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Chest X-ray and CT findings Unilateral pneumonia Bilateral pneumonia Multiple mottling and ground- glass opacity			X-ray			X-ray	CT-Scan - - +								CT-Scan							CT-Scan - - +
Treatment																						
Oxygen therapy	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air
								Remdesivir D1	Remdesivir D2	Remdesivir D3	Remdesivir D4	Remdesivir D5	Remdesivir D6	Remdesivir D7	Remdesivir D8	Remdesivir D9	Remdesivir D10					
Remdesivir								Loading dose									Last dose					

ND = not determined

Table S3-3 - Case #3 - Baseline characteristics and their changes over time

Case #3	January 25 Illness day 4	January 26 Illness day 5	January 27 Illness day 6	Diagnostic day January 28 Illness day 7	January 29 Illness day 8	January 30 Illness day 9	January 31 Illness day 10	February 1 Illness day 11	February 2 Illness day 12	February 3 Illness day 13	February 4 Illness day 14	February 5 Illness day 15	February 6 Illness day 16	February 7 Illness day 17	February 8 Illness day 18	February 9 Illness day 19	February 10 Illness day 20	February 11 Illness day 21	February 12 Illness day 22	February 13 Illness day 23	February 14 Illness day 24
Setting	WARD	WARD /ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU	ICU
Symptoms											NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Any of the following symptoms	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fever	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Highest temperature, °C	37.2	38.5							36.9	36.4	36.8	37.4	36.3	35.9	36.5	38	38.5	37.6	39.2	38.4	35.8
Cough	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Shortness of breath	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fever, cough, shortness of breath	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chest pain	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Diarrhea	+	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Headache	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Myalgia or fatigue	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sore throat	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Rhinorrhea	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nausea and vomiting	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Conjunctivitis	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pleural effusion	-	-	-	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Biological variables																					
White blood cell counts, 10 ⁹ /L	8.0	8.0	ND	11.1	12.2	18.6	20	22.6	13.6	19.4	18.8	11.3	8.3	6	7.9	8.8	12.2	19.1	30.8	28.9	28.9
Neutrophil count, 10 ⁹ /L	ND	7.2	ND	ND	11.5	17.2	18.9	21.3	12.7	18.4	17.6	10.4	7.7	5.3	6.6	6.7	8.7	15	23.6	19.6	20
Lymphocyte count, 10 ⁹ /L	ND	ND	ND	ND	0.3	0.5	0.4	0.4	0.3	0.4	0.6	0.1	0.3	0.6	0.6	1.4	2.6	3.3	6.4	8.8	7.5
Hemoglobin, g/l	12.3	12.3	ND	12.3	10.2	11.2	9.7	10	6.3	10.9	11.7	8.5	8.7	7.4	9.6	8.2	10.1	9.9	9.6	8.7	9.6
Platelet count, 10 ⁹ /L	134	134	ND	126	108	136	61	62	34	51	21	37	27	53	66	40	102	45	4.9	17	97
Prothrombin time, s	ND	ND	ND	ND	24	26	25	24	26	24	24	26	21	21	21	23	2.4		21	21	26
Albumin, g/L	ND	ND	ND	ND	21	21	18	17	23	21	19	16	14	20	21	22	22		18	22	23
Creatinine kinase, UI/L	ND	ND	ND	ND	47	47	34	38	39	82	84	157	294	294	561	558	474		329	251	448
Alanine aminotransferase, UI/L	21	21	ND	416	555	504	319	245	106	83	63	33	27	28	36	51	54	ND	87	77	57
Aspartate aminotransferase, U/L	66	66	ND	1636	>2000	1255	485	21.3	81	101	95	62	95	96	137	ND	187	ND	226	206	ND
Total bilirubin, mmol/L	ND	13	ND	ND	15	22	21	24	26	41	70	61	55	74	103	ND	161	ND	217	280	ND
Sodium, mmol/L	136	136	ND	144	144	140	139	136	141	139	137	135	136	136	135	146	139	ND	138	134	138
Potassium, mmol/L	3.2	3.2	ND	3.5	4.6	5.2	5.4	5.2	5.3	4.5	4.4	3.8	ND	4.6	5	ND	4.9	ND	4.8	5.2	ND
Urea, mmol/L	8	8.2	ND	9	12.1	18.1	14.5	27.6	9.8	9.1	10.1	8.3	4.1	4.6	8	5	13.2	ND	8.2	22.6	9.1
Creatinine, µmol/L	92	92	ND	209	350	438	293	402	170	142	147	137	114	107	129	134	ND	ND	ND	ND	ND
C-reactive protein mg/L	123+	ND	ND	ND	199	>200	138	103	41	52	157	179	> 200	138	189	159	176	ND	91	58	29
Lactate UI/L	ND	1.5	ND	7.6	2.3	3	5.8	4	3.1	1.6	1.8	1.9	2.1	3.8	2.1	1.9	3.0	4.8	4.5	5.5	8.8
Chest X-ray and CT findings	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray	X-ray
Unilateral pneumonia	+	+																			
Bilateral pneumonia																					
Multiple mottling and ground-glass opacity			ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS	ARDS
Viral treatment	NONE	NONE	NONE		Remdesivir Loading dose	None	None	None	None	None	None	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose	Remdesivir maintenanc e dose
Supportive treatment																					
Oxygen therapy	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Non-invasive mechanical ventilation	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mechanical ventilation	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vasopressors	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal replacement therapy	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

ND = not determined; NA = not applicable; ARDS = acute respiratory distress syndrome

Table S3-4 - Case #4 - Baseline characteristics and their changes over time

Case #4	Diagnosis day January 24 Illness day 2	January 25 Illness day 3	January 26 Illness day 4	January 27 Illness day 5	January 28 Illness day 6	January 29 Illness day 7	January 30 Illness day 8	January 31 Illness day 9	February 1 Illness day 10	1 st Asymptomatic day February 2 Illness day 11	February 3	February 4	February 5	February 6	February 7	February 8	February 9	February 10	February 11	February 12 Discharge day
Setting	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD					
Symptoms																				
Any of the following symptoms	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Highest temperature, °C	37.7°C	37.1°C	38.0°C	37.7°C	37.6°C	36.5°C	37.1°C	36.7°C	36.8°C	36.5°C	36.5°C	36.5	37.1	37	37.2	36.9	36.8	37.2	37.1	37.1
Cough	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-
Shortness of breath	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever, cough, shortness of breath	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia or fatigue	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rhinorrhea	+	+	+	+	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea and vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biological variables																				
White blood cell counts, 10 ⁹ /L	ND	3.3	ND	ND	2.6	ND	2.3	3.5	2.7	ND	3.9	4.2	ND	3.8	ND	ND	5.3	ND	4.8	ND
Neutrophil count, 10 ⁹ /L	ND	ND	ND	ND	1	ND	0.8	1.4	1	ND	2	2.3	ND	1.8	ND	ND	3.1	ND	2.8	ND
Lymphocyte count, 10 ⁹ /L	ND	1.2	ND	ND	1.5	ND	1.4	1.7	1.4	ND	1.5	1.6	ND	1.7	ND	ND	2.1	ND	1.7	ND
Hemoglobin, g/l	ND	13	ND	ND	13.7	ND	13.2	12.7	12.5	ND	12.3	12.3	ND	15.2	ND	ND	11.7	ND	11.2	ND
Platelet count, 10 ⁹ /L	ND	195	ND	ND	180	ND	172	168	172	ND	196	252	ND	208	ND	ND	303	ND	296	ND
Prothrombin time, s	ND	20	ND	ND	20	ND	18	ND	20	ND	22	20	ND	19	ND	ND	20	ND	ND	ND
Albumin, g/L	ND	37	ND	ND	36	ND	35	34	34	ND	34	25	ND	33	ND	ND	32	ND	ND	ND
Creatinine kinase, UI/L	ND	88	ND	ND	72	ND	49	56	48	ND	63	27	ND	58	ND	ND	39	ND	ND	ND
Alanine aminotransferase, UI/L	ND	42	ND	ND	35	ND	28	39	44	ND	62	56	ND	71	ND	ND	94	ND	ND	ND
Aspartate aminotransferase, U/L	ND	46	ND	ND	36	ND	35	33	53	ND	53	49	ND	63	ND	ND	65	ND	ND	ND
Total bilirubin, mmol/L	ND	9	ND	ND	9	ND	9	9	10	ND	10	13	ND	9	ND	ND	11	ND	ND	ND
Sodium, mmol/L	ND	142	ND	ND	140	ND	140	135	140	ND	138	133	ND	134	ND	ND	135	ND	ND	ND
Potassium, mmol/L	ND	4.5	ND	ND	4.1	ND	4.5	4.7	4.3	ND	4.1	4.4	ND	46	ND	ND	4	ND	ND	ND
Urea, mmol/L	ND	2.9	ND	ND	3.6	ND	3.3	3.6	3.8	ND	3.7	3.8	ND	38	ND	ND	4	ND	ND	ND
Creatinine, μmol/L	ND	38	ND	ND	36	ND	60	41	59	ND	21	31	ND	68	ND	ND	43	ND	ND	ND
C-reactive protein	ND	<5	ND	ND	<5	ND	<5	<5	<5	ND	<5	<5	ND	<5	ND	ND	<5	ND	ND	ND
Lactate UI/L	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Chest X-ray and CT findings		X-ray		X-ray		X-ray	CT		X-ray		X-ray	X-ray								
Unilateral pneumonia		-		-		-	+		-		-	-								
Bilateral pneumonia		-		-		-	-		-		-	-								
Multiple mottling and ground-glass opacity		-		-		-	-		-		-	-								
Viral treatment	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
Oxygen therapy	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air

ND = not determined; NA = not applicable

Table S3-5 - Case #5 - Baseline characteristics and their changes over time

Case #5	January 28 Illness day 1	Diagnostic day January 29 Illness day 2	January 30 Illness day 3	January 31 Illness day 4	1 st Asymptomatic day February 1 Illness day 5	February 2	February 3	February 4	February 5	February 6	February 7	February 8	February 9	February 10	February 11	February 12	From February 13 to February 17 (discharge day)
Setting	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD	WARD
Symptoms																	
Any of the following symptoms	+	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Highest temperature, °C	37.4	38.0	37	37.2	37.4	36.8	37.1	37.1	36.9-	36.9-	37.1	36.9	37	37.2	36.9	37	36.8
Cough	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-	-	-
Shortness of breath	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fever, cough, shortness of breath	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Headache	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Myalgia or fatigue	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rhinorrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nausea and vomiting	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Odynophagia	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Biological variables																	
White blood cell counts, 10 ⁹ /L	ND	ND	3.1	ND	ND	3.6	ND	2.5	ND	4	ND	4.4	ND	3.5	ND	4.5	ND
Neutrophil count, 10 ⁹ /L	ND	ND	1.7	ND	ND	2.3	ND	1	ND	2.5	ND	2.8	ND	1.9	ND	2.4	ND
Lymphocyte count, 10 ⁹ /L	ND	ND	1.3	ND	ND	1.1	ND	1.3	ND	1.3	ND	1.3	ND	1.3	ND	1.2	ND
Hemoglobin, g/l	ND	ND	13.2	ND	ND	13.3	ND	11.6	ND	12	ND	12.5	ND	10	ND	11.8	ND
Platelet count, 10 ⁹ /L	ND	ND	18.4	ND	ND	164	ND	151	ND	195	ND	227	ND	233	ND	275	ND
Prothrombin time, s	ND	ND	20	ND	ND	18	ND	22	ND	22	ND	21	ND	20	ND	Nd	ND
Albumin, g/L	ND	ND	40	ND	ND	32	ND	32	ND	33	ND	35	ND	30	ND	32	ND
Creatinine kinase, UI/L	ND	ND	66	ND	ND	68	ND	33	ND	<5	ND	7	ND	7	ND	64	ND
Alanine aminotransferase, UI/L	ND	ND	11	ND	ND	32	ND	26	ND	56	ND	56	ND	46	ND	46	ND
Aspartate aminotransferase, U/L	ND	ND	29	ND	ND	68	ND	36	ND	46	ND	68	ND	49	ND	61	ND
Total bilirubin, mmol/L	ND	ND	10	ND	ND	11	ND	10	ND	11	ND	13	ND	14	ND	9	ND
Sodium, mmol/L	ND	ND	139	ND	ND	139	ND	40	ND	139	ND	140	ND	134	ND	137	ND
Potassium, mmol/L	ND	ND	4	ND	ND	3.7	ND	3.8	ND	4.1	ND	4.2	ND	2.8	ND	ND	ND
Urea, mmol/L	ND	ND	3.3	ND	ND	4.6	ND	4	ND	3.1	ND	4.1	ND	5.5	ND	4.6	ND
Creatinine, µmol/L	ND	ND	66	ND	ND	68	ND	59	ND	61	ND	67	ND	67	ND	73	ND
C-reactive protein mg/L	ND	ND	<5	ND	ND	<5	ND	<5	ND	ND	ND	ND	ND	<8	ND	<5	ND
Lactate UI/L	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Chest X-ray and CT findings				X-ray		X-ray	CT scan										
Unilateral pneumonia				-		-	-										
Bilateral pneumonia				-		-	-										
Multiple mottling and ground-glass opacity				-		-	+										
Viral treatment	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE	NONE
Oxygen therapy	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air	Ambient air

ND = not determined; NA = not applicable